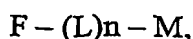


Patent Claims

1. A fusion protein of the structure



- 5 having essentially the same biological specificity and activity of human TPO, comprising an immunoglobulin heavy chain constant region (F) and a human TPO molecule (M) in a truncated (1 – 174) form modified by one or more amino acid substitutions, wherein said fusion protein is substantially non-immunogenic or less immunogenic than the parental fusion protein comprising the non-modified human TPO, and said amino acid substitutions
10 have been carried out in one or more of the sequence tracks

(i) GEWKTQMEETKAQDILGAVTLLLEGVM,

(ii) PTTAVPSRTSLVLTLL

- within the truncated wild-type TPO molecule and cause a reduction or an elimination of one or more of T-cell epitopes, which act in the parental non-modified fusion molecule as
15 MHC class II binding ligands and stimulate T-cells, said immunoglobulin heavy chain constant region is fused directly ($n = 0$) or indirectly ($n = 1$) via a linker molecule (L) to said modified human TPO molecule (M).

2. A fusion protein according to claim 1, wherein F is an Fc domain.

3. A fusion protein of claim 1 or 2, wherein F comprises a hinge region.

4. A fusion protein according to any of the claims 1 – 3, wherein the C-terminus of the human immunoglobulin heavy constant region domain is linked directly or indirectly to the N-
25 terminus of the modified TPO molecule.

5. A fusion protein according to any of the claims 1 – 4, wherein said modified TPO molecule contains one or more of the amino acid substitutions
M55K, A60R and V161A
30 within the sequence tracks (i) – (ii).

6. A fusion protein according to any of the claims 1 – 4, wherein said TPO molecule in said fusion protein has the formula / structure:

SPAPPACDLRVLSKLLRDSHVLHSRLSQCPVHPLPTFVLLPAVDFSLGX¹X²KTQX³EEX⁴KX⁵X⁶D
 X⁷LGAX⁸TX⁹LX¹⁰X¹¹GVMAARGQLGPTCLSSLLGQLSGQVRLLLGALQSLTQLPPQGRTTAHKDP
 NAIFLSFQHLLRGKVRFLMLVGGSTLCVRRAPPTTAX¹²X¹³SRTSLVLTINEL

X¹ is A, E;

5 X² is S, W;

X³ is A or T or K, S or M;

X⁴ is A, T;

X⁵ is R, A;

X⁶ is A or T or Q;

10 X⁷ is A or T or I;

X⁸ is A or T or V;

X⁹ is A or T or S or L;

X¹⁰ is A or L;

X¹¹ is A or S or E;

15 X¹² is N or A or T or R or E or D or G or H or P or K or Q or V;

X¹³ is A or P,

and whereby simultaneously X¹ = E, X² = W, X³ = M, X⁴ = T, X⁵ = A, X⁶ = Q, X⁷ = I,
 X⁸ = V, X⁹ = L, X¹⁰ = L, X¹¹ = E, X¹² = V and X¹³ = P are excluded.

20 7. A fusion protein according to any of the claims 1 – 6, wherein F is in Fc domain of human IgG4.

8. A fusion protein according claim 7, wherein L is a peptide linker having 4 – 20 amino acid residues.

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9. A fusion protein according to any of the claims 1 – 8, selected from the group consisting of
 F – M1 to F – M67,

F – L – M1 to F – L – M67, and

F1 – L – M1 to F1 – L1 – M67,

30

wherein F is an immunoglobulin heavy chain constant region, L is a linker peptide, F1 is a Fc domain of human IgG4 comprising a modified hinge region, L1 is a peptide linker having the sequence GAGGGGSGGG GSGGGSG, and M1 – M67 are modified TPO sequences as specified in Table A1.

10. A fusion protein according to claim 9 selected from the group consisting of
F - M1, F - L - M1, F1 - L1 - M1
F - M66, F - L - M66, F1 - L1 - M66, and
F - M67, F - L - M67, F1 - L1 - M67.
- 5
11. A dimeric fusion protein comprising two identical monomeric fusion protein chains according to any of the claims 1 - 10.
12. A peptide molecule selected from the group consisting of
- 10 (i) GEWKTQMEETKAQDILGAVTLLLEGVM,
(ii) PTTAVPSRTSLVLT
- or a sequence track consisting of at least 9 consecutive amino acid residues of any of said peptide molecules having a potential MHC class II binding activity and created from the primary sequence of non-modified human TPO, whereby said peptide molecule or
- 15 sequence track has a stimulation index of > 1.8 in a biological assay of cellular proliferation and said index is taken as the value of cellular proliferation scored following stimulation by a peptide and divided by the value of cellular proliferation scored in control cells not in receipt peptide.
- 20 13. Use of a peptide molecule according to claim 12 for the manufacture of a vaccine in order to reduce immunogenicity to TPO in a patient.
14. A peptide molecule modified by one or more amino acid substitutions deriving from any peptide molecule according to claim 11 and having a reduced or absent potential MHC
- 25 class II binding activity expressed by a stimulation index of less than 2, whereby said index is taken as the value of cellular proliferation scored following stimulation by a peptide and divided by the value of cellular proliferation scored in control cells not in receipt peptide.
15. Use of a modified peptide molecule according to claim 14 for the manufacture of a modified TPO molecule M1 to M67 of Table A1, or a fusion protein comprising an Fc
- 30 portion of an immunoglobulin and said modified TPO molecule.